Multivariable models of outcomes with [^{177}Lu]Lu-PSMA-617: analysis of the phase 3 VISION trial

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Summary

Background **[^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolonged life in patients with metastatic castration-resistant prostate cancer (mCRPC) in VISION (NCT03511664). However, distinguishing between patients likely and unlikely to respond remains a clinical challenge. We present the first multivariable models of outcomes with ^{177}Lu-PSMA-617 built using data from VISION, a large prospective phase 3 clinical trial powered for overall survival.**

Methods **Adults with progressive post androgen receptor pathway inhibitor and taxane prostate-specific membrane antigen (PSMA)-positive mCRPC received ^{177}Lu-PSMA-617 plus protocol-permitted standard of care (SoC) or SoC alone. In this *post hoc* analysis, multivariable Cox proportional hazards models of overall survival (OS) and radiographic progression-free survival (rPFS), and a logistic regression model of prostate-specific antigen response (≥50% decline; PSA50) were constructed and evaluated using C-index or receiver operating characteristic (ROC) analyses with bootstrapping validation. Nomograms were constructed for visualisation.**

Findings **Patients were randomised between June 2018 and October 2019. Data from all 551 patients in the ^{177}Lu-PSMA-617 arm were analysed in multivariable modelling. The OS nomogram (C-index, 0.73; 95% confidence interval [CI], 0.70–0.76) included whole-body maximum standardised uptake value (SUV_{max}), time since diagnosis, opioid analgesic use, aspartate aminotransferase, haemoglobin, lymphocyte count, presence of PSMA-positive lesions in lymph nodes, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and neutrophil count. The rPFS nomogram (C-index, 0.68; 0.65–0.72) included SUV_{max}, time since diagnosis, opioid analgesic use, lymphocyte count, presence of liver metastases by computed tomography, LDH, and ALP. The PSA50 nomogram (area under ROC curve, 0.72; 95% CI, 0.68–0.77) included SUV_{max}, lymphocyte count and ALP. Performances of the OS and rPFS models were maintained when they were reconstructed excluding SUV_{max}.**

Interpretation **These models of outcomes with ^{177}Lu-PSMA-617 are the first built using prospective phase 3 data. They show that a combination of pretreatment laboratory, clinical, and imaging parameters, reflecting both patient**

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and tumour status, influences outcomes. These models are important for aiding treatment selection, patient management, and clinical trial design.

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Keywords: Overall survival; Radiographic progression-free survival; PSA response; Nomogram; ^{177}Lu-PSMA-617; VISION trial; mCRPC

Research in context

Evidence before this study

[^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolongs life in patients with late-stage metastatic castration-resistant prostate cancer (mCRPC). However, outcomes with ^{177}Lu-PSMA-617 can vary and predictors of response are important for informing treatment selection and patient expectations. We used the term "(metastatic castration-resistant prostate cancer) AND (177Lu-PSMA-617 OR lutetium-177) AND (nomogram OR predictive OR prognostic) NOT review[pt]" to search PubMed for English language publications from January 1, 2014 to March 20, 2024. We found 22 publications reporting on studies of potential pretreatment parameters that are predictive or prognostic of response to ^{177}Lu-PSMA-617 in patients with mCRPC. Of these, 15 analysed retrospective data. The remaining seven publications reported data from small (n = 14 to n = 68) prospective observational, phase 2, or pilot studies. We found no models of outcomes with ^{177}Lu-PSMA-617 in patients with mCRPC based on pretreatment parameters recorded as part of large prospective phase 3 clinical trials.

Added value of this study

We built the first models of treatment outcomes with ^{177}Lu-PSMA-617 based on data from a large international prospective phase 3 clinical trial (VISION). The models combine multiple pretreatment parameters that are readily available in most real-world clinical settings to provide probabilities of PSA response, radiographic progression-free survival, and overall survival. We confirmed that in addition to PSMA positron emission tomography (PET) imaging parameters, which have previously been identified as being prognostic for outcomes with radioligand therapy, several other laboratory and clinical parameters influence outcomes.

Implications of all the available evidence

These models are important for aiding clinical decision-making and supporting discussions with patients around treatment expectations. The results of this analysis of robust prospective phase 3 trial data are supportive of some previous small and/or retrospective studies that have identified parameters that associate with treatment outcomes. However, we also provide evidence that, in addition to PSMA PET parameters, several other pretreatment parameters are associated with outcomes and may be useful for informing treatment selection.

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is an incurable and fatal disease.[1] [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolongs life in patients at the end stages of the disease.[2] However, outcomes with any given therapy vary considerably and there is currently no way to predict which patients will respond well and which patients are unlikely to respond to treatment with ^{177}Lu-PSMA-617. Reliable models to predict treatment outcomes with ^{177}Lu-PSMA-617 are needed to aid clinical decision-making, treatment selection, and to manage patient expectations.[3] Such models are only as good as the data from which they derive. To date, there is no model for predicting treatment outcomes with PSMA-targeted radioligand therapy in patients with mCRPC that utilises data from a prospective, randomised, phase 3 study that has a definitive clinical endpoint, such as overall survival. Previous models have been based on studies that are small, retrospective, involved multiple therapeutics and/or have had other deficiencies, such as assessing a limited range of parameters.[4–11] There is an unmet clinical need for a model that is based on a high quality, randomised, trial data.

VISION was a large, prospective randomised phase 3 clinical trial of ^{177}Lu-PSMA-617 that led to market approval in the USA[12] and Europe.[13] In that trial, ^{177}Lu-PSMA-617 plus protocol-permitted standard of care (SoC) was shown to prolong survival, delay radiographic progression, extend time to first symptomatic skeletal event and maintain quality of life compared with SoC alone.[2,14] The trial was powered for both primary endpoints of OS and rPFS.[2] Here, we comprehensively assessed a combination of pretreatment imaging, clinical and laboratory parameters collected in VISION for association with clinically relevant patient outcomes in

an effort to understand the variables that may inform clinical decision-making and treatment selection.

Methods

Study design and participants

This was a *post hoc* analysis of the international, multicentre, randomised phase 3 VISION study of ^{177}Lu-PSMA-617 in patients with mCRPC (ClinicalTrials.gov: NCT03511664; EudraCT Number: 2018-000459-41). In VISION, 831 adults with progressive prostate-specific membrane antigen (PSMA)-positive mCRPC were randomised to receive ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for ≤ six cycles) plus protocol-permitted SoC (n = 551) or SoC alone (n = 280), as previously described.[2] Randomisation was stratified by baseline lactate dehydrogenase level (≤260 U/mL or >260 U/mL), presence of liver metastases (yes or no), ECOG performance status (0–1 or 2) and inclusion of androgen receptor pathway inhibitors (ARPIs) in SoC at the time of randomisation (yes or no). Eligible patients must have previously received at least one ARPI and one or two taxane regimens. PSMA positivity was determined by [^{68}Ga]Ga-PSMA-11 (^{68}Ga-PSMA-11) positron emission tomography/computed tomography (PET/CT) examined by a central reader. Patients were enrolled if they had at least one PSMA-positive metastatic lesion with ^{68}Ga-PSMA-11 uptake greater than that of liver parenchyma by visual assessment and no PSMA-negative lesions meeting specific size exclusion criteria as detailed previously.[2] Full eligibility criteria, patient disposition, and baseline characteristics have been published previously.[2]

The objective of this study was to build nomograms for clinical outcomes in patients receiving ^{177}Lu-PSMA-617 plus SoC.

VISION was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent. At each trial site, independent ethics review boards approved the trial protocol.

Outcomes

The study outcomes assessed were OS (defined as time from randomisation to death from any cause), rPFS (defined as time from randomisation to independently centrally reviewed disease progression as per the Prostate Cancer Clinical Trials Working Group 3 criteria[15] or death), and PSA50 (defined as PSA decline ≥50% from baseline). Events and censoring related to these endpoints have been published previously.[2]

Statistical analyses

Clinical parameters

Twenty-nine pretreatment parameters were extracted from VISION data; pre-established cut-points were used for categorical parameters (Table 1).[16–20] Parameters evaluated included those identified in published

Category	Parameter and cut points (where applicable)		Value
Characteristics of patients at baseline	Age, years, median (IQR)		71 (65, 75)
	ECOG performance status, n (%)	2	63 (8)
		0/1	768 (92)
Prior treatment	Number of prior systemic treatments, median (IQR)		5 (4, 7)
	Number of prior taxanes, n (%)	1	481 (58)
		>1	350 (42)
	Number of prior ARPIs, n (%)	1	426 (51)
		>1	405 (49)
	Opioid analgesic use, n (%)	Yes	430 (52)
		No	401 (48)
Baseline clinical chemistry and laboratory parameters	Albumin, g/L, median (IQR)		39 (36, 42)
	Alkaline phosphatase,[19] U/L, n (%)	≥140	312 (38)
		<140	518 (62)
		N/A	1 (<1)
	Aspartate a minotransferase, U/L, median (IQR)		24 (18, 33)
	Haemoglobin, g/L, median (IQR)		117 (105, 129)
	Lactate dehydrogenase,[18] U/L, n (%)	≥280	263 (32)
		<280	567 (68)
		N/A	1 (<1)
	Lymphocyte count, cells/L, median (IQR)		1.025 (0.760, 1.455)
	Monocyte count, cells/L, median (IQR)		0.5 (0.40, 0.65)
	Neutrophil count,[20] cells/L, n (%)	≥7 × 10^9	85 (10)
		<7 × 10^9	705 (85)
		N/A	41 (5)
	Neutrophil-to-lymphocyte ratio,[16,17] n (%)	≥3	522 (63)
		<3	266 (32)
		N/A	43 (5)
	Pan-immune-inflammation value, median (IQR)		452.12 (252.26, 856.73)
	Platelets, U/μL, median (IQR)		230 (189.5, 279)
	PSA, ng/mL, median (IQR)		76 (20.45, 282.2)
	White blood cell count, cells/L, median (IQR)		6.1 (4.72, 7.5)
PSMA PET parameters	PSMA-positive tumour volume, median (IQR)		426.02 (140.66, 1210.90)
	Whole-body [^{68}Ga]Ga-PSMA-11 tumour SUV_{mean}, median (IQR)		7.55 (5.76, 9.93)
	Whole-body [^{68}Ga]Ga-PSMA-11 tumour SUV_{max}, median (IQR)		34.39 (20.44, 52.87)

(Table 1 continues on next page)

Category	Parameter and cut points (where applicable)		Value
(Continued from previous page)			
Location and extent of disease	Presence of PSMA-positive lesions in bone, n (%)	Yes	761 (91)
		No	65 (8)
		N/A	5 (<1)
	Presence of PSMA-positive lesions in liver, n (%)	Yes	109 (13)
		No	717 (86)
		N/A	5 (<1)
	Presence of PSMA-positive lesions in lymph nodes, n (%)	Yes	559 (67)
		No	267 (32)
		N/A	5 (<1)
	Presence of PSMA-positive lesions in soft tissue, n (%)	Yes	334 (40)
		No	492 (59)
		N/A	5 (<1)
	Presence of liver metastases by CT, n (%)	Yes	124 (15)
		No	687 (83)
		N/A	20 (2)
	Number of metastatic lesions, n (%)	>20	312 (38)
		≤20	435 (52)
		N/A	84 (10)
	Time since prostate cancer diagnosis, years, median (IQR)		7.42 (4, 11.83)

Cut points for parameters that were assessed categorically are indicated. ARPI, androgen receptor pathway inhibitor; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; PET, positron emission tomography; N/A, not available; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SUV, standardised uptake value.

Table 1: **Parameters included in the development of VISION nomograms.**

literature[4,5,11,21,22] as being potentially associated with mCRPC outcomes (provided they were available and relevant to the VISION population), as well as the PSMA PET imaging parameters and the randomisation stratification parameters used in VISION. The models were not further adjusted for the VISION stratification parameters. Maximum standardised uptake value (SUV_{max}) and mean SUV (SUV_{mean}) were calculated for the whole body. Definitions for PSMA PET imaging-related parameters are described briefly in the Supplementary material.

Single pretreatment parameter modelling

Models including single pretreatment parameters were constructed with data from both arms of the VISION full analysis set (n = 831). Associations between each parameter and outcomes were assessed with Cox proportional hazard (OS and rPFS) or logistic regression (PSA50) models. Each parameter was evaluated for associations with outcomes in the overall population independent of treatment type, and for statistical interaction between treatment with ^{177}Lu-PSMA-617 plus SoC and parameter status, according to:

$$Y \sim X + Treatment \text{ (for associations in overall population)}$$

$$Y \sim X \times Treatment \text{ (for treatment effect)}$$

where Y is the outcome variable; X is the given biomarker covariate; and *Treatment* is the binary covariate for treatment arms. The p values for the X term in overall population association modelling and the X : *Treatment* term in treatment effect modelling were corrected for multiplicity using false discovery rate q values (a = 0.05).

Multivariable modelling and VISION nomogram construction

Models including multiple pretreatment parameters were constructed with ^{177}Lu-PSMA-617 arm data only (n = 551). To reduce redundancy, Spearman's rank correlation was performed to identify highly correlated parameters; only one from each pair of co–linear parameters was included in subsequent parameter selection for each multivariable model. Bayesian parameter selection using horseshoe priors analysis[23] was used to select parameters for inclusion in the multivariable models and was implemented using the brms package in R.[24] Multivariable Cox proportional hazards (OS and rPFS) and logistic regression (PSA50) models were built with the selected parameters. Nomograms were constructed for visualisation of each multivariable model. Accuracies of the models were evaluated with C-index (for OS and rPFS models) or receiver operating characteristic (ROC) (for the PSA50 model) analyses; 95% confidence intervals (CIs) were calculated using bootstrapping.[25] Following initial model development, nomograms were reconstructed excluding SUV_{max} to assess the impact on model performance. A C-index or area under the ROC curve of 0.5 indicates a model with predictive accuracy equivalent to random chance and 1 indicates perfect predictive accuracy.[26] Performances of the models were compared using the DeLong method for comparing the area under the curves.[27]

Application of Gafita et al. (2021) nomograms to VISION data

The methods for the development of the Gafita et al. (2021) nomograms have been previously published.[4] Patients in VISION were assigned risk scores for OS, rPFS and PSA50 according to the equations derived by Gafita et al. (2021)[4] and were then stratified into lower-risk and higher-risk groups according to previously determined optimal cut points. The cut points were determined using log-rank statistics, implemented using the *cutp* function in the SurvMisc package in R,[28] to provide the largest discrepancy between the risk groups for OS and PSA-PFS. The PSA-PFS Gafita et al. (2021) nomogram was used to assign risk scores for rPFS for

VISION data. Hazard ratios (HRs) and 95% CIs were calculated using the Kaplan–Meier method.

Role of the funding source

Representatives from Novartis, in collaboration with the authors, were involved in the study design, collection, analysis, and interpretation of the data, and the writing and review of the manuscript.

Results

Single pretreatment parameter modelling

In single pretreatment parameter analyses, 22 parameters (76%) were associated with OS in the overall VISION population; 21 (72%) and 10 (34%) were associated with rPFS and PSA50, respectively (Table S1). Higher levels of alkaline phosphatase (ALP), aspartate aminotransferase (AST) and lactate dehydrogenase, and presence of liver metastases were associated with worse OS, rPFS and PSA50. Conversely, higher haemoglobin and neutrophil counts, higher SUV_{mean} and SUV_{max}, and longer time since prostate cancer diagnosis were associated with better OS, rPFS and PSA50. Fewer parameters were associated with differential outcomes after treatment with ^{177}Lu-PSMA-617 plus SoC versus SoC alone (Table S2). Higher SUV_{max} or SUV_{mean} were associated with higher PSA50 response rates in the ^{177}Lu-PSMA-617 plus SoC arm versus the control arm, but no parameters were statistically significantly associated with improved OS or rPFS in the ^{177}Lu-PSMA-617 plus SoC arm versus the control arm.

Multivariable modelling

Spearman's rank correlation analysis identified co-linearity between three pairs of parameters: neutrophil-to-lymphocyte ratio (NLR) and pan-immune-inflammation value (Spearman correlation: 0.77); neutrophil count and white blood cell count (0.94); and SUV_{mean} and SUV_{max} (0.82). NLR, neutrophil count, and SUV_{max} were included in parameter selection analyses for multivariable model building; models including SUV_{mean} are included in the Supplementary Materials.

In horseshoe priors analysis, parameters with effect size 80% Bayesian credible intervals that did not overlap zero were selected for inclusion in the multivariable models. In the analysis including SUV_{max}, of 29 pretreatment parameters assessed, 10 parameters for OS, seven for rPFS, and three for PSA50 were identified for inclusion in the multivariable models and nomogram construction (Fig. 1). The C-index for the OS model was 0.73 (95% CI, 0.70–0.76) (Fig. 2); the C-index for the rPFS model was 0.68 (0.65–0.72) (Fig. 3). The area under the ROC curve for the PSA50 model was 0.72 (95% CI, 0.68–0.77) (Fig. 4). Model performances were

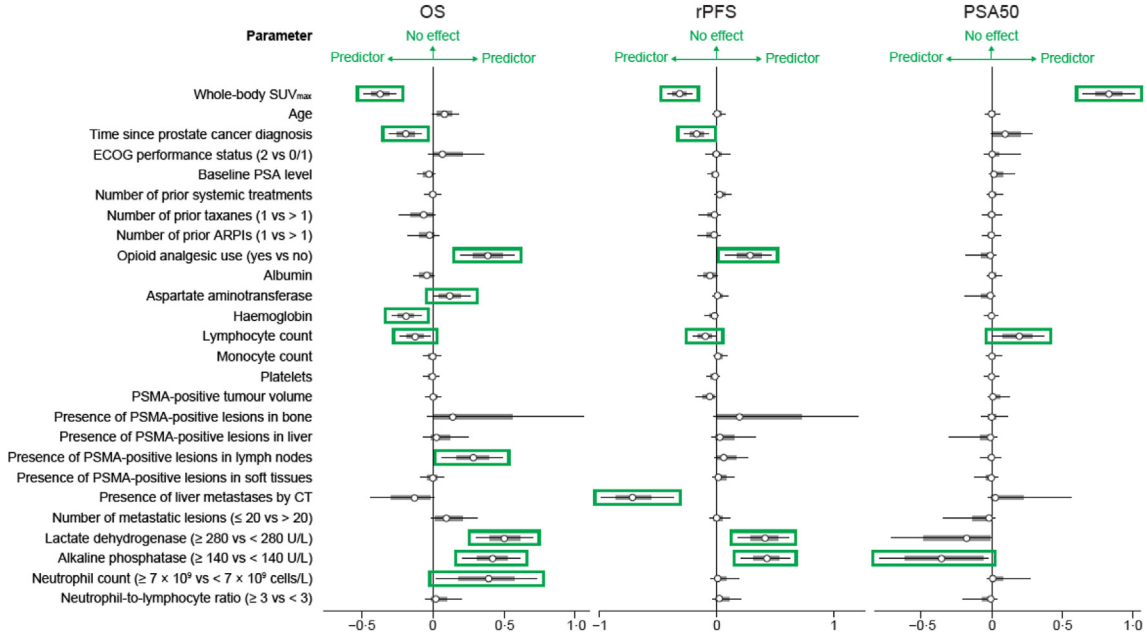

Fig. 1: **Bayesian parameter selection using horseshoe priors analysis with SUV_{max}, including ^{177}Lu-PSMA-617 arm data only.** Dots represent point estimates for the given variable. Box and whiskers represent 50% and 80% Bayesian credible intervals, respectively. Green boxes indicate parameters significantly associated with given outcome. X-axis indicates coefficient value in model. ARPI, androgen receptor pathway inhibitor. CT, computed tomography. ECOG, Eastern Cooperative Oncology Group. OS, overall survival. PSA, prostate-specific antigen. PSA50, prostate-specific antigen response (≥50% decline). PSMA, prostate-specific membrane antigen. rPFS, radiographic progression-free survival. SUV_{max}, maximum standardised uptake value.

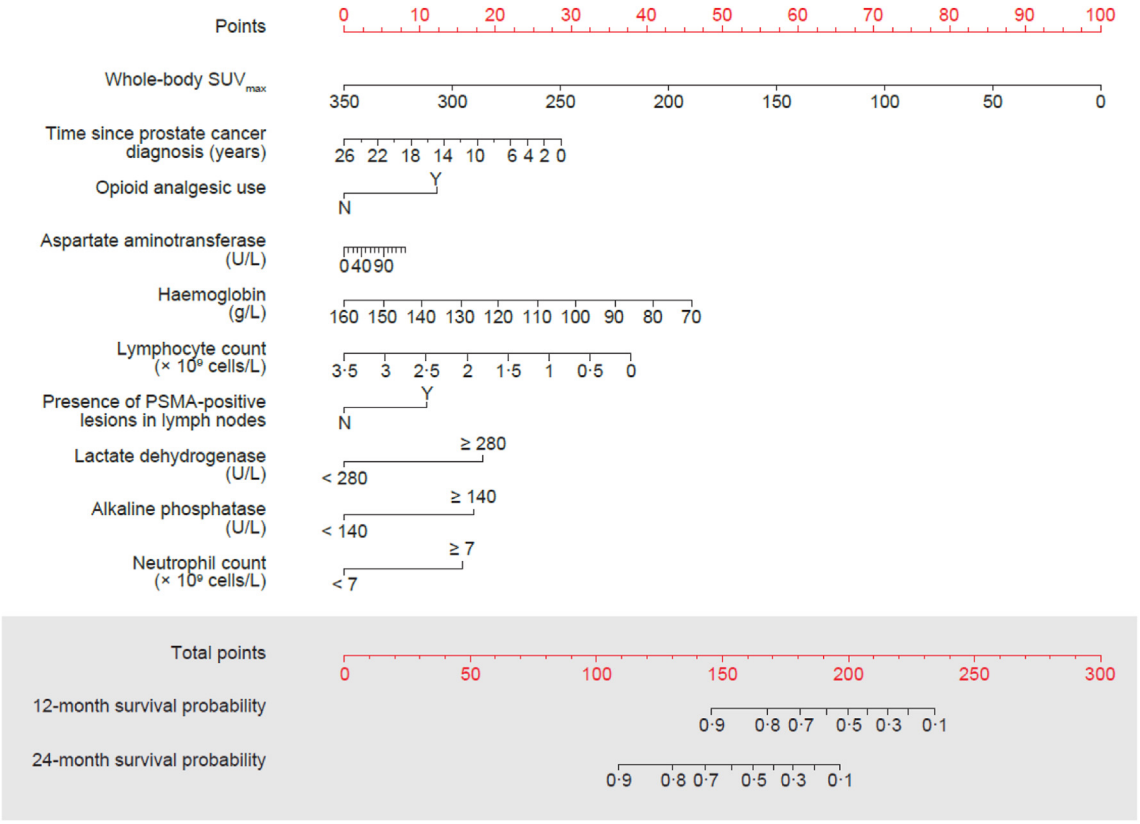

***Fig. 2:* VISION overall survival nomogram, including ^{177}Lu-PSMA-617 arm data only**. The value of each pretreatment parameter (listed on the left) indicates a certain number of points according to the alignment with the points scale at the top of the nomogram. Points for all parameters are summed to provide a total points score (red line in grey box).[40] The total points score corresponds to respective 12- and 24-month survival probabilities. The C-index was 0.73 (95% CI, 0.70–0.76). CI, confidence interval; PSMA, prostate-specific membrane antigen; SUV_{max}, maximum standardised uptake value.

similar when SUV_{mean} (Figures S1–S4 and Table S3) was included in the horseshoe priors analysis instead of whole-body SUV_{max}.

When the models were reconstructed excluding SUV_{max}, the C-indices remained similar for the OS (0.73 [95% CI, 0.70–0.76]) (Figure S5 and Table S3) and rPFS (0.67 [0.63–0.70]) (Figure S6 and Table S3) models. However, the area under the ROC curve for the PSA50 model decreased (0.64 [95% CI 0.59–0.69]) (Figure S7 and Table S3).

Application of Gafita et al. (2021) nomograms to VISION data

When applied to VISION data, the OS nomogram developed by Gafita et al. (2021)[4] was able to stratify VISION patients from both arms into lower-risk and higher-risk groups with a C-index of 0.67 (Figure S8A). The PSA-PFS nomogram developed by Gafita et al. (2021)[4] was able to stratifiy VISION patients receiving ^{177}Lu-PSMA-617 plus SoC into rPFS lower-risk and higher-risk groups, but for those receiving SoC alone there was no difference in rPFS between those classified as lower- or higher-risk (Figure S8B). The rPFS model C-index was 0.61. The PSA50 nomogram developed by Gafita et al. (2021)[4] was able to predict outcomes in the ^{177}Lu-PSMA-617 plus SoC arm in VISION with reasonable accuracy but was less accurate for the VISION control arm (Table S4).

Discussion

^{177}Lu-PSMA-617 is an effective treatment for prolonging life in patients with mCRPC who have previously received ARPI and taxane therapy.[2] However, not all patients respond equally well to ^{177}Lu-PSMA-617 treatment and it is crucial to distinguish those who are most likely to respond from those who are not. Here, we developed multivariable models of PSA response (PSA50), durability of response (rPFS), and survival (OS) after treatment with ^{177}Lu-PSMA-617, and presented the data as nomograms for ease of clinical interpretation. These multivariable models of treatment outcomes are the first to be built using data from a prospective, randomised, phase 3, clinical trial of ^{177}Lu-PSMA-617, which was powered for OS and rPFS as the

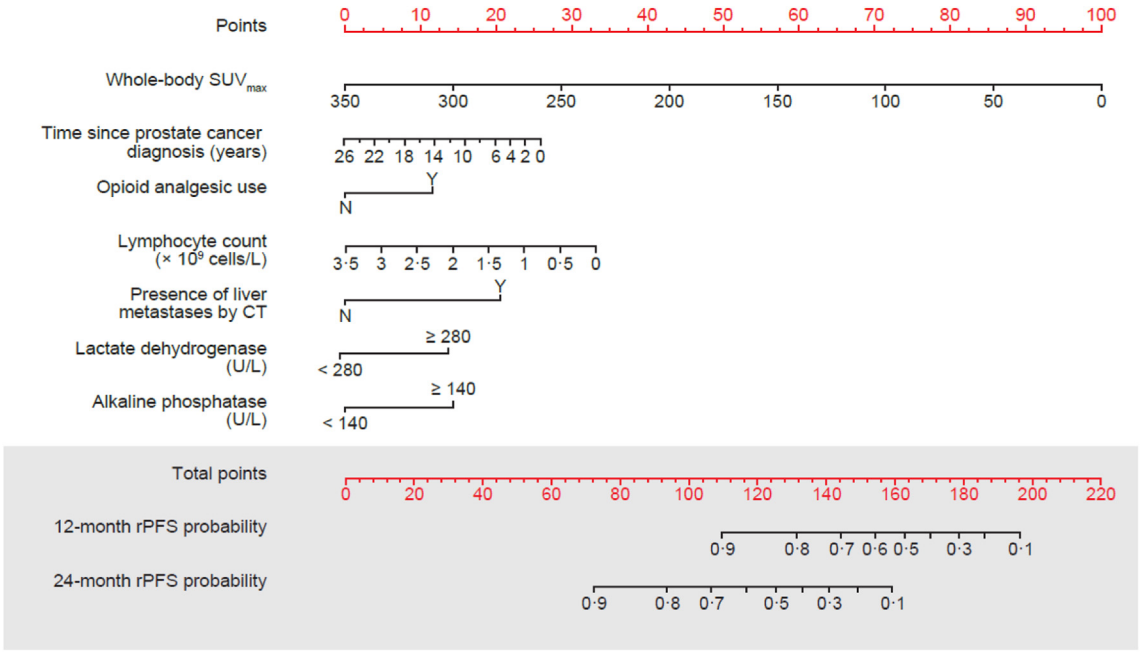

Fig. 3: **VISION radiographic progression-free survival nomogram, including ^{177}Lu-PSMA-617 arm data only**. The value of each pretreatment parameter (listed on the left) indicates a certain number of points according to the alignment with the points scale at the top of the nomogram. Points for all parameters are summed to provide a total points score (red line in grey box).[40] The total points score corresponds to respective 12- and 24-month rPFS probabilities. The C-index was 0.68 (95% CI, 0.65–0.72). CI, confidence interval; CT, computed tomography; rPFS, radiographic progression-free survival; SUV_{max}, maximum standardised uptake value.

alternate primary endpoints and led to market approval in the USA and Europe.[2] VISION provided data on a wide range of clinical parameters from a large and relatively homogeneous patient population all receiving ^{177}Lu-PSMA-617, in contrast to previous models of ^{177}Lu-PSMA outcomes, which were built using retrospective datasets[4–7] and/or were small cohort studies,[8,9] and in some cases included data on more than one radioligand therapy.[4]

These models have several important clinical implications. The nomograms can be used to inform discussions with patients and manage expectations of outcomes with ^{177}Lu-PSMA-617. In conjunction with physician expertise and experience, these nomograms

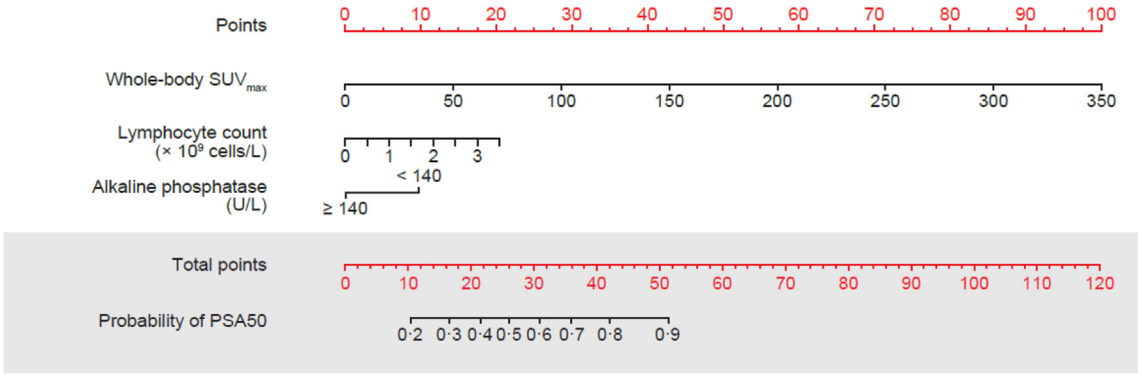

Fig. 4: **VISION prostate-specific antigen response nomogram, including ^{177}Lu-PSMA-617 arm data only**. The value of each pretreatment parameter (listed on the left) indicates a certain number of points according to the alignment with the points scale at the top of the nomogram. Points for all parameters are summed to provide a total points score (red line in grey box).[40] The total points score corresponds to PSA50 probability. The area under the ROC curve was 0.72 (95% CI, 0.68–0.77). CI, confidence interval; PSA50, prostate-specific antigen response (≥50% decline); ROC, receiver operating characteristic; SUV_{max}, maximum standardised uptake value.

can be used as a tool to identify patients most likely or unlikely to respond to ^{177}Lu-PSMA-617 to inform treatment selection, as well as to identify patients likely to benefit from treatment combination regimens. Finally, the nomograms could be used in clinical trial patient selection to enrich the trial population with patients most likely to respond to treatment, reducing the required sample size and minimising drug exposure in patients unlikely to benefit.

We assessed practical and clinical pretreatment parameters based on patient, tumour, and imaging characteristics that should be easily utilised in most clinical settings. Imaging parameter tumour SUV_{max} was preferentially included in the nomograms over SUV_{mean} because of the relatively greater clinical availability of SUV_{max}. Both parameters inform on PSMA expression but calculation of SUV_{mean} requires tumour quantification tools that are not widely implemented in clinical practice. Models including SUV_{mean} performed with similar accuracy to those including $SUV_{max.}$ Nomograms were also reconstructed excluding SUV_{max} to provide a nomogram that could be employed in settings where PSMA PET analysis is not available. PSMA expression is an important parameter because it both characterises the degree of differentiation of the tumour and influences absorbed radiation dose. Higher levels of tumour PSMA expression are thought to enhance the effectiveness of PSMA radioligand therapy by leading to increased uptake and delivery of radiation to metastatic lesions. This model is supported by several studies of ^{177}Lu-PSMA-617. In the TheraP trial,[29] for ^{177}Lu-PSMA-617 versus cabazitaxel, patients with SUV_{mean} ≥10 had PSA50 of 91% versus 47% and those with SUV_{mean} <10 had PSA50 of 52% versus 32%.[30] Similarly, in a substudy of VISION, higher versus lower SUV_{mean} was shown to be strongly associated with improved rPFS and OS outcomes in patients treated with ^{177}Lu-PSMA-617 versus SoC.[31] This sub-study also showed that, although the magnitude of the benefit was greater at higher SUV_{mean} values, no optimal cut point could be derived,[32] leading to SUV_{max} being treated as a continuous variable in the current study. In the single pretreatment parameter analyses presented here, SUV_{mean} and SUV_{max} associated with OS, rPFS, and PSA50 in the overall population, but were only associated with differential treatment outcomes for PSA50. The multivariable models of OS, rPFS, and PSA50 all included SUV_{max}, but other factors were also associated with outcomes and model performances were maintained when SUV_{max} was removed from the OS and rPFS nomograms. These results suggest that, in addition to PSMA PET parameters, clinical parameters are associated with survival outcomes and may be useful for helping to inform treatment selection.

We aimed to provide models that included the minimum number of pretreatment parameters to maximise the accuracy and real-world clinical utility of the nomograms. For this reason, the single pretreatment parameter modelling and Bayesian parameter selection included the VISION randomisation stratification parameters, but the models were not further adjusted for these parameters. In single pretreatment parameter analyses, several pretreatment parameters were identified as having an association with one or more outcomes. NLR was associated with OS and rPFS in the overall population but not with PSA50, consistent with published literature.[33,34] Higher versus lower levels of liver enzymes ALP and AST and having versus not having liver metastases were associated with poorer patient outcomes. Having received one versus two prior taxanes correlated with better OS and rPFS outcomes, supportive of a previous subgroup analysis of VISION.[35]

For multivariable analyses, more parameters were found to be associated with OS and rPFS in horseshoe priors analyses than with PSA50. The results suggest that a broad picture of patient health and disease, indicated by factors including time since prostate cancer diagnosis, opioid analgesic use, and clinical chemistry parameters, in addition to imaging parameters, is needed to predict mid-to long-term outcomes (i.e. OS and rPFS). Age may also affect OS, but should not dictate treatment selection, in agreement with recommendations from the International Society of Geriatric Oncology.[36] In contrast, shorter-term outcomes (PSA50) may be primarily driven by PSMA expression, indicated by measures such as SUV_{max}. The reduction in model performance upon reconstruction of the PSA50 nomogram excluding SUV_{max} is supportive of this hypothesis.

Previous studies have identified clinical and imaging parameters associated with prostate cancer outcomes,[3,30,31] and multivariable models of outcomes after radioligand therapy have been built using phase 2 and real-world data.[4,5,9,10,37] In a retrospective study of patients with mCRPC receiving ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T as part of phase 2 clinical trials or compassionate access programmes in Germany, the USA, and Australia, Gafita et al. (2021) developed prognostic nomograms for overall survival (OS), prostate-specific antigen-progression-free survival (PSA-PFS; primary outcomes), and PSA response (PSA50; secondary outcome).[4] Similarly, Gaal et al. (2023) constructed a nomogram for OS with retrospective data from patients with mCRPC treated with ^{177}Lu-PSMA-617 in one hospital in Berlin.[5] However, the retrospective nature of these analyses may have limited their performance and introduced bias.

The VISION nomograms showed some consistency with previously published nomograms. The VISION and Gafita et al. (2021)[4] OS nomograms both included time since diagnosis, haemoglobin, and a PSMA PET imaging parameter, while overlapping parameters in the rPFS/PSA-PFS nomograms were time since diagnosis, liver metastases, and a PSMA PET imaging parameter.

However, the Gafita et al. (2021)[4] nomograms were based on a smaller sample size (n = 196) than VISION, 20% of patients had not received prior chemotherapy, 8% had not received prior ARPI, median treatment cycles was three (versus five in VISION), and data collected with both ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T were assessed. When applied to the VISION population, the nomograms presented in this paper performed with higher accuracy than the equivalent nomograms developed by Gafita et al. (2021). In an OS nomogram constructed by Gaal et al. (2023),[5] the De Ritis ratio (AST/alanine transaminase) was found to be an important clinical parameter, and haemoglobin and NLR also showed an association with OS in univariate analyses.[5] These results are supportive of the VISION OS nomogram, which included AST, haemoglobin, neutrophil count, and lymphocyte count. However, the Gaal et al. (2023)[5] data set was based on a small sample size (n = 93), 36% of patients had not received prior chemotherapy, the median number of treatment cycles was three, and patients received a different dosing schedule versus VISION (6.0 GBq every 8 weeks versus 7.4 GBq every 6 weeks).

There were several limitations associated with this *post hoc* analysis of VISION. Firstly, the models were built with clinical trial data and will need to be validated in a real-world setting.[38] Secondly, it was not possible to take into account individual variations in radiosensitivity. Thirdly, it was not possible to generate a validation cohort because of the small sample sizes for some parameters. Instead, bootstrapping[25] was used for internal validation, which has been found to be an effective method for estimating model accuracy and is associated with low bias.[39] A fourth limitation is that we did not aim to develop nomograms to predict outcomes in patients receiving SoC alone, but only in those receiving ^{177}Lu-PSMA-617 plus SoC. Finally, the results should not be generalised to patients with PSMA-negative lesions because these patients were excluded from VISION, and to patients in earlier disease stages than those in VISION.

In conclusion, multivariable models of OS, rPFS, and PSA50 in patients with PSMA-positive mCRPC receiving ^{177}Lu-PSMA-617 plus SoC were constructed in the first such analysis of a large, prospective, randomised, phase 3, clinical trial. The resulting nomograms are a useful and important tool for clinical decision-making, informing patient discussions, and research design. The models demonstrate that many laboratory, clinical, and imaging parameters are associated with outcomes in patients with mCRPC.

Contributors

KH, AG, JSdB, OS, KNC, BJK, KR, STT, CCW, ZZ, OM, MJM, and KF were involved in the conception, design, or planning of the study. KH, JSdB, OS, KNC, BJK, KR, STT, JC, GEH, OM, MJM, and KF collected the data. KH, AG, JSdB, OS, KNC, BJK, KR, STT, CCW, ZZ, OM, MJM, and KF analysed the data. KH, AG, MJM and KF accessed and verified the data. All authors were involved in interpreting the data, critical review of all versions of the manuscript, and are accountable for all aspects of the work.

Data sharing statement

Novartis is committed to sharing access to anonymised patient level data and clinical study reports from eligible studies with qualified external researchers. All data provided are anonymised to respect the privacy of patients who have participated in the trials in line with applicable laws and regulations. For more detailed information and to make a request, please view https://www.clinicalstudydatarequest.com/.

Declaration of interests

KH reports receiving grants or contracts from Boston Scientific, Janssen, and Novartis; consulting fees from Amgen, AstraZeneca, Bain Capital, Bayer, Boston Scientific, Convergent, Curium, Debiopharm, EcoR1, Fusion, GE Healthcare, Immedica, Isotopen Technologien München, Janssen, Merck, Molecular Partners, Novartis, NVision, POINT Biopharma, Pfizer, Radiopharm Theranostics, Rhine Pharma, Siemens Healthineers, Sofie Biosciences, Telix, Theragnostics, and ymabs; and stock or other ownership in AdvanCell, Aktis Oncology, Convergent, NVision, Pharma 15, and Sofie Biosciences. **JSdB** reports receiving grants or contracts from Amgen, Astellas, AstraZeneca, Bayer, Bioxcel Therapeutics, Crescendo, Daiichi-Sankyo, Endocyte, Genentech/Roche, GlaxoSmithKline, ImCheck Therapeutics, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, and Sanofi Aventis; consulting or advisory fees from Astellas, AstraZeneca, Bayer, Daiichi-Sankyo, Genentech/Roche, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Orion, Pfizer, Sanofi Aventis, and Taiho; payment or honorarium from Astellas, AstraZeneca, Bayer, Cellcentric, Crecendo, Daiichi, Genentech, Genmab, GlaxoSmithKline, Janssen, Merck Serono, Mycrix, MSD, Orion, Pfizer, Sanofi Aventis, and Taiho; being an inventor on patent 8,822,438; participating on a data safety monitoring or advisory board for Amgen, AstraZeneca, Bayer, Bioxcel Therapeutics, Crescendo, Daiichi-Sankyo, Endocyte, Genentech/Roche, GlaxoSmithKline, ImCheck Therapeutics, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Oncternal, Pfizer, and Sanofi Aventis; and receiving institutional royalties or licenses related to abiraterone, PARP inhibitor, and PI3K/AKT. **OS** reports receiving support for the present manuscript from Novartis; institutional grants or contracts from Amgen, AstraZeneca, Bayer, Endocyte, Invitae, Janssen, Lantheus, Merck, Novartis, Progenics, and Tenebio; consulting fees from ARTBIO, AstraZeneca, Bayer, Blue Earth Diagnostics, Clarity Pharmaceuticals, Fusion, Isotopen Technologien Muenchen, Janssen, Merck, Myovant, Myriad, Noria Therapeutics, NorthStar, Novartis, Pfizer, POINT Biopharma, Sanofi, Telix, and Tenebio; travel and accommodation expenses from Lantheus, NorthStar, and Novartis; participation on a data safety monitoring or advisory board for AstraZeneca, Merck, and Pfizer; and stock or stock options in ARTBIO, Clarity Pharmaceuticals, Convergent, Fusion, Lilly, Pfizer, Ratio, and Telix. **KNC** reports receiving grants or contracts from AstraZeneca, Bayer, Janssen, Merck, Novartis, Pfizer, POINT Biopharma, and Roche; and consulting fees from Astellas, AstraZeneca, Bayer, Janssen, Merck, Novartis, Pfizer, POINT Biopharma, and Roche. **BJK** reports receiving consultant or advisory fees from Bayer, Isotope Technologies Munich, and Novartis; and research funding from Novartis. **KR** reports receiving consultant fees from ABX, ABX-CRO, Amgen, Bayer Healthcare, Janssen Cilag, Novartis, and Sirtex; and lecture payments from AstraZeneca, Bayer Healthcare, Novartis, and Siemens Healthcare. **STT** reports receiving institutional fees from AbbVie, Ambrx, Amgen, Astellas, AstraZeneca, Aveo, Bayer, Bristol Myers Squibb, Clarity, Clovis, Endocyte, Genentech, Gilead, Inovio, Janssen, Karyopharm, Medivation, Merck, Newlink, Novartis, POINT Biopharma, Rexahn, Sanofi, and Seattle Genetics; and consultant fees from AbbVie, Aikido Pharma, Ambrx, Amgen, Astellas, Bayer, Blue Earth, Clarity Pharma, Clovis, Convergent Therapeutics, Daiichi Sankyo, Eisai, EMD Serono, Genentech, Genomic Health, Janssen, Medivation, Merck, Myovant, Novartis, Pfizer, POINT Biopharma, Regeneron, Sanofi, Seattle Genetics, Telix, Tolmar, and TransThera. **JC** reports stock or other ownership interest in Sofie

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102862.

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